REMARKS

Claims 72 and 74 - 91 are pending in the current application. Claims 1-71 and 73 were previously cancelled.

Rejection under 35 USC §103 - Claims 72 and 74-91 under 35 USC §103 as unpatentable over Kosal in view of Bott et al. and Woodward et al.

In the most recent Office Action, the rejection based on Kosal, Bott, and Woodward has been maintained. Applicants submit that the rejection is flawed, and that all remaining claims are patentable over the applied references.

Kosal is directed to silicone pressure sensitive adhesive compositions which comprise a disperse silicone phase in a continuous aqueous phase, i.e., and oil-in-water emulsion. Kosal lists a number of different possible uses for the adhesive including

> "paper coatings, such as adhesive labels and sealing strips, in adhesive modifiers such as release modifying additives for organic pressure sensitive adhesives, in personal care applications to give greater durability, protective qualities, water resistance and barrier properties, for example in eye cosmetics such as mascara and in sunscreen formulations as described in U.S. Pat. No. 5,451,610, and in medical applications such as transdermal drug delivery patches, described for example in U.S. Pat. No. 5,162,410, or to hold an active material such as a fungicide to the skin surface. The avoidance of hydrocarbon based solvents is generally desirable in medical and personal care applications, and also in paper coating applications where evaporation of organic solvent can be a fire hazard." [col. 5, lines 17-30]

None of these many possible uses describe an adhesive composition containing a protein active agent. Rather, Kosal is directed to a silicone-based pressure sensitive adhesive. However, the rejection is based on the argument that one skilled in the art would have been motivated "to combine the teachings of Kosal and Bott et al. and prepare O/W emulsions comprising the hydrophobic phase with silicone PSA taught by Kosal for transdermal delivery of protein active agents." The Examiner found "motivation" in Kosal's teaching of providing "controlled tack and lubrication and greater durability, free of hydrocarbon based solvents, and enables holding of the active agent to the skin" (Action, p. 5).

Kosal does not teach or suggest the controlled release of an active agent.

Applicants disagree with the Examiner's interpretation of Kosal with respect to any teaching concerning controlled release of an active agent. Specifically, applicants' claims are directed to a controlled-release composition and method of delivery. As described in the specification, the term "controlled-release" is defined to mean that the active agent is released in a controlled manner over time ("sustained release") from the composition (see, e.g., Examples 1-8).

(1) Kosal is silent concerning any controlled release properties of his pressure sensitive adhesive composition. That is to be expected, as the Kosal specification is directed primarily to the adhesive composition and its properties, and not to any specific active agents which may be released over time. Applicants also note that the Examiner has dropped her reliance on Kosal's mention, at col. 5, line 18, that the described pressure sensitive adhesives may find use "as release modifying additives for organic pressure sensitive adhesives." As previously explained, that mention must be understood in proper context to be directed to the ability of the adhesive compositions, when blended with other "organic"-based adhesives, to modify the *adhesive release characteristics* of those adhesives which has nothing whatsoever to do with controlling the release of an active agent contained within the adhesive.

(2) Kosal's only mention of the use of an active agent in conjunction with the pressure adhesive composition is at col. 5, where it is stated that the adhesive may find use as a transdermal drug delivery *patch* or may be used to *hold* a fungicide to the skin surface. However, these are descriptions of using the adhesive composition as a covering or dressing to secure contact of an active agent against the skin. This is in contrast to the claimed controlled release composition in which the protein active agent is in the continuous hydrophilic phase of an oil-in-water emulsion.

(3) By contrast, Bott teaches placing an active agent in the discontinuous phase of a water-in-oil emulsion. Thus, the Bott composition is not only very different from the presently-claimed composition, it differs significantly from Kosal. Unlike Kosal, Bott

teaches the use of a *continuous* silicone phase ("silicone matrix") and a *discontinuous* aqueous phase which would be understood by persons skilled in the art to be a water-in-oil composition in which the hydrophilic carrier containing the active agent is dispersed throughout a silicone matrix (see, e.g., para. [0008]).

Thus, in Bott's preparation, a hydrophilic phase containing the active agent and hydrophilic carrier is emulsified with a silicone phase to produce discrete droplets of the aqueous phase dispersed into a continuous silicone phase. The emulsion is then cast and dried, resulting in droplets of the aqueous phase containing the active agent entrapped within the continuous silicone phase. Bott suggests that several mechanisms could be involved in controlling the release of the active agent from the preparation including the addition of hydrophilic agents to the silicone phase or choosing a silicone having a low cross-link density. See, e.g., paras. [0035] and [0058]. As applicants noted in their previous response, the two compositions, and their respective mechanisms for controlling the release of active agent, are quite different.

(4) There is a material difference between locating an active agent in an oil-in-water emulsion to control the release of that agent (claimed invention) versus simply holding an active agent against a patient's skin (Kosal). Prolonged contact is not the same as controlled release. The attempt to conflate the two ("Kosal's composition is useful in preparations for prolonged or sustained active agent release" [Action at p. 9]) lacks any evidentiary basis. Kosal is silent concerning how long or sustained any release of any active agent might be.

(5) Kosal does not address, nor does he solve, any problem relating to the controlled release of an active agent from an adhesive composition. The presence of a thickening agent in Kosal's adhesive teaches nothing about the controlled release of an active agent. The assertion at page 11 of the Action, that persons skilled in the art would appreciate that Kosal's use of a thickening agent "modifies release of the active agent, e.g., a fungicide," is speculation, not evidence. Nothing in Kosal teaches this. To the contrary, Kosal simply states that the pressure sensitive adhesive will "hold" the

active agent to the skin. There is absolutely no statement in any way relating the presence of an optional thickening agent to the control of the release of an active agent.

Further, the statement at page 11 of the Action that, "absent evidence, it is not seen that the composition of Kosal et al. prepared by phase inverting the composition of Bott et al. would result in a different mechanism, not rate, of release control," contains both factual and legal error. Initially, it is not an applicant's burden to provide evidence to negate obviousness; to the contrary, it is the Office's legal burden to establish evidence that supports the conclusion of obviousness. And, the facts in this instance are explicit and clear. Bott states that the mechanisms for release of the active agent from the water-in-oil composition are the creation of "pores, crevices, cracks, or fissures within the silicone matrix," or the presence of hydrophilic agents in the silicone phase, or the choice of a silicone having a low crosslink density (paragraphs [0035] and [0058]). These are certainly statements of different *mechanisms* for release of the active agent than that described by applicants. Kosal's only description of the use of an active, as discussed above, is to use the pressure sensitive adhesive to cover an active and hold it against the surface of the skin. Thus, the facts (as opposed to speculation) are that Bott teaches a different mechanism and Kosal is silent.

(6) Applicants are not attacking the references individually (see, Action at page 10). The legal evidentiary burden is on the Office to establish facts that support the conclusion that not only would one skilled in the art be motivated to combine references teachings, but also that there would be a reasonable expectation of success in doing so. Applicants submit that that evidentiary burden has not been carried because the reference teachings are not combinable in the manner proposed, and even if combined would not result in the claimed invention.

The Examiner's asserted "motivation" for combining reference teachings involves Kosal's statements regarding the properties of the pressure sensitive adhesive (Action at page 5). None of those statements supports the conclusion that the skilled person would be motivated to combine the reference teachings as none of these properties relate to the controlled release of an active agent from the composition.

(a) "controlled tack and lubrication" – This statement relates to the use of Kosal's pressure sensitive adhesive in paper coatings for adhesive labels and envelope sealing strips (col. 5, lines 14-17). These properties have nothing to do with the controlled release of any active agent.

(b) "greater durability" – This statement is with respect to "personal care compositions" (col. 5, lines 19-20) such as "mascara" and "sunscreen formulations" and their "durability" on the skin of a user. These properties have nothing to do with the controlled release of an active agent.

(c) "free of hydrocarbon based solvents" – This is taught to be "desirable," not required, (col. 5, lines 27-30), for some uses of the adhesive. Again, there is no teaching that this property has any effect on the release of an active agent from the composition.

(d) "holding of the active agent to the skin surface" – This would be an expected property of a pressure sensitive adhesive. Again, however, the terms "prolonged" and "controlled release" have been equated when the record is clear that they are not. As discussed above, the two words have different meanings and would be so understood by persons skilled in this art.

(e) Kosal's oil-in-water emulsion results from the inversion of a water-in-oil emulsion – In general, this is a conventional method for making an oil-in-water emulsion. However, the fact that Bott is a water-in-oil emulsion provides no motivation "to combine Kosal and Bott et al" (Action at page 11). Applicants fail to see the factual basis for any motivation for Kosal to use Bott's emulsion, especially where Kosal is directed to a pressure sensitive adhesive and Bott, primarily, is not. While Kosal does teach a phase inversion technique, that technique is performed with no active agent in the aqueous phase because Kosal has no need for any active agent.

When stripped of all speculation, the rejection is that a skilled person, without knowledge of the claimed invention, would look to a pressure sensitive adhesive composition (Kosal) which does not even address the problem of providing the controlled release of a protein active agent, and then modify that pressure sensitive adhesive composition by substituting a water-in-oil emulsion (Bott) that does use a protein active agent and inverting it into an oil-in water emulsion to form a pressure

sensitive adhesive that contains a protein active agent. The rejection is based on speculation and prohibited hindsight.

Applicants submit that this rejection is flawed factually and legally for the many reasons discussed above. Independent claim 72 is patentable over Kosal and Bott. As for dependent claims 74-86, applicants submit that as they depend directly or indirectly from patentable independent claim 72, those claims are patentable for the same reasons that claim 72 is patentable as discussed in detail above. Further, as claim 90 recites a method of using the composition of claim 72, claim 90 is patentable for the same reasons that claim 72 is patentable.

With respect to claims 87-88 which are directed to a multi-layer dressing, the Examiner has cited to Woodard et al. (US 4655767) for its teaching of a transdermal drug delivery device having multiple layers. The rejection does not explicitly provide a motivation for combining the reference teachings other than to allude to the rejection of claim 72 over Kosal and Bott and the fact that Woodard evidences that three-layer transdermal drug delivery devices were known in the art (Action, p. 6). Nor were any specific modifications or substitutions proposed for any of the compositions of Kosal or Bott or the construction of Woodard.

It is apparent that Kosal's adhesive could be used as adhesive layer 22 in Woodard, but that substitution does not meet the claims. Applicants also note that in Woodard, the active agent (drug) is located in elastomer layer 20, not adhesive layer 22. Based on the rejection of claim 72, from which claims 87-88 depend, it was proposed to include the active agent of Bott in the pressure sensitive adhesive of Kosal. But so modifying those references would render layer 20 in Woodard superfluous. Applicants also note that while Woodard teaches that the device 10 is adhered to a patient's skin, nowhere in the passage at col. 3, lines 13-27 is it stated that such pressure causes the "drug-impregnated elastomer layer" to come into contact with the skin as alleged by the Examiner (Action at page 13). As best understood, even if the reference teachings were to be combined in the manner proposed by the Examiner (which manner has certainly not been made clear in any of the Actions), the construction would be different than the subject matter of claims 87-88.

Finally, with respect to the rejection of claim 89, it is clear that Kosal does not teach or suggest a controlled release layer free of water. Indeed, as discussed above, Kosal is silent concerning any controlled release of an active agent that his adhesive may or may not include. And, while Bott teaches an embodiment using a dry patch, again, Bott teaches a water-in-oil emulsion, not an oil-in-water emulsion. The reference teachings are not combinable in the manner proposed by the Examiner. Even if those teachings were to be combined, the claimed subject matter would not result because Bott, which is the only reference that relates to the controlled release of an active agent, explicitly teaches one to use a water-in-oil emulsion.

Conclusion

Applicants submit that for all of the reasons discussed above, the rejections are not well taken and should be withdrawn. It is believed that the above represents a complete response to the rejections set forth in the Official Action, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,

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